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CLINICAL INVESTIGATION **Gastrointestinal Cancer**

PET-BASED TREATMENT RESPONSE EVALUATION IN RECTAL CANCER: PREDICTION AND VALIDATION

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Purpose: To develop a positron emission tomography (PET)-based response prediction model to differentiate pathological responders from nonresponders. The predictive strength of the model was validated in a second patient group, treated and imaged identical to the patients on which the predictive model was based.
Methods and Materials: Fifty-one rectal cancer patients were prospectively included in this study. All patients underwent fluorodeoxyglucose (FDG) PET-computed tomography (CT) imaging both before the start of chemoradiotherapy (CRT) and after 2 weeks of treatment. Preoperative treatment with CRT was followed by a total mesorectal excision. From the resected specimen, the tumor regression grade (TRG) was scored according to the Mandard criteria. From one patient group (n = 30), the metabolic treatment response was correlated with the pathological treatment response, resulting in a receiver operating characteristic (ROC) curve based cutoff value for the reduction of maximum standardized uptake value (SUV_{max}) within the tumor to differentiate pathological responders (TRG 1–2) from nonresponders (TRG 3–5). The applicability of the selected cutoff value for new patients was validated in a second patient group (n = 21).
Results: When correlating the metabolic and pathological treatment response for the first patient group using ROC curve analysis (area under the curve = 0.98), a cutoff value of 48% SUV_{max} reduction was selected to differentiate pathological responders from nonresponders (specificity of 100%, sensitivity of 64%). Applying this cutoff value to the second patient group resulted in a specificity and sensitivity of, respectively, 93% and 83%, with only one of the pathological nonresponders being false positively predicted as pathological responding.
Conclusions: For rectal cancer, an accurate PET-based prediction of the pathological treatment response is feasible already after 2 weeks of CRT. The presented predictive model could be used to select patients to be considered for less invasive surgical interventions or even a "wait and see" policy. Also, based on the predicted response, early modifications of the treatment protocol are possible, which might result in an improved clinical outcome.

Locally advanced rectal cancer, Chemoradiotherapy, Sequential PET-CT imaging, Pathological response prediction, TRG.

INTRODUCTION

Over the past several years, the reduction of the metabolic activity of rectal tumors during preoperative treatment, assessed with repeated positron emission tomography (PET)-computed tomography (CT) imaging, has been shown to accurately predict the pathological treatment response (1–14). Most of the published studies about PET-based treatment response predictions determined a (receiver operating characteristic [ROC] curve based) cutoff value, percent reduction of the mean, or maximum standardized uptake value (SUV_{max}) within the tumor after finishing preoperative treatment, to differentiate pathological responders from nonresponders. However, also early metabolic treatment responses within the tumor, as early as 2 weeks after the start of preoperative treatment, were presented as a strong predictor of the pathological treatment response (9, 10, 12). Two studies even presented early PET-based response predictions as being more accurate when compared to response predictions based

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on pre- and posttreatment PET-imaging (9, 12). A prediction of the pathological treatment response early during preoperative treatment is more attractive for clinical practice, because this enables individualized treatment schemes in the near future, possibly resulting in an improved tumor control or modified surgical approaches like less invasive or delayed surgery in combination with an intensive imaging follow-up.

The main objective of a PET-based predictive model is the actual prediction of the pathological treatment response for patients not included in the patient group on which the model is based. However, so far, none of the presented PET-based response predictive models was yet validated with a secondary patient group. Because for further development and clinical usefulness of PET-based response predictive models a proper validation with a secondary group is required, this study was undertaken to develop a PET-based prediction model to differentiate pathological responders from nonresponders. The predictive strength of the presented predictive model was validated in a second patient group, treated, and imaged identical to the patients on which the predictive model was based.

METHODS AND MATERIALS

Patient Characteristics

Fifty-one patients diagnosed with locally advanced rectal cancer were included in this study, from which the clinical TN staging was evaluated on a pretreatment magnetic resonance scan (Table 1). All patients were preoperatively treated with radiotherapy (28 fractions of 1.8 Gy, 5 fractions/week) and concomitant chemotherapy (capecitabine 825 mg/m^2 twice daily, 7 days per week), followed by a total mesorectal excision approximately 3 months after the start of preoperative treatment (Fig. 1). Radiotherapy treatment was delivered by four beams, anteroposterior, posteroanterior, and left and right lateral, each with an energy of 10 MV. For each patient, a three-dimensional (3D) conformal plan was made according to the International Commission on Radiation Units and Measurements specifications. As a part of the study, all patients underwent fluorodeoxyglucose (FDG) PET-CT imaging both before the start of CRT and at the end of the second week of treatment (Fig. 1). According to the Dutch law, the Medical Ethics Committee approved the trial. All patients gave written informed consent before entering the study.

PET-CT imaging and processing

All PET-CT scans were performed using a dedicated Siemens Biograph 40 TruePoint PET-CT simulator (Siemens Medical, Erlangen, Germany) with an axial field of view of 16.2 cm, slice thickness of 3 mm, and a pixel spacing of 5.3456 mm in both directions. The scanner is equipped with ultrafast detector electronics (Pico3D) and has a spatial resolution of approximately 6-mm full-width-at-half-maximum. PET imaging was performed in 3D, requiring a proper scatter correction. CT-based attenuation and decay correction was performed. PET images were reconstructed from the acquired list-mode data using Fourier-rebinning and ordered-subset-expectation-maximization-reconstruction (OSEM 2D) with four iterations and eight subsets. After a fasting period of at least 6 h, FDG was injected intravenously, with the activity normalized for the weight of the patient (weight [kg]*4 + 20) [MBq]). After an uptake period of 60 min, PET acquisition was started with the patient positioned equal to the radiotherapy treatment position using a movable laser alignment system.

Table 1. Overview of the clinical staging (cTNM), the tumor regression grade (TRG), and the response index (RI) of SUV_{max} after 2 weeks of preoperative chemoradiotherapy

Patient no.	cTNM	TRG	RI SUV_{max} (%)	Patient no.	cTNM	TRG	RI SUV_{max} (%)
1	T2N1M0	1	51.9	1	T4N1M0	3	47.6
2	T3N2M0	3	41.7	2	T3N1M0	3	−9.2
3	T3N2M0	2	69.4	3	T3N0M0	1	62.5
4	T4N2M0	2	38.9	4	T4N1M0	4	16.9
5	T3N1M0	2	64.8	5	T3N2M0	1	69.1
6	T3N2M0	3	31.5	6	T3N0M0	4	−19.9
7	T3N1M0	3	−11.8	7	T3N2M0	4	2.9
8	T3N2M0	3	47.6	8	T2N1M0	2	55.9
9	T3N2M0	4	14.4	9	T3N2M0	4	10.6
10	T3N1M0	1	70.4	10	T3N1M0	3	54.4
11	T3N2M0	4	28.8	11	T3N1M0	1	45.3
12	T3N1M0	3	40.8	12	T3N2M0	3	40.0
13	T3N0M0	3	4.1	13	T3N1M0	4	15.0
14	T3N2M0	3	35.9	14	T3N2M0	4	45.1
15	T3N2M0	3	33.6	15	T2N0M0	3	1.2
16	T3N2M0	4	28.6	16	T3N2M0	2	63.2
17	T3N2M0	1	54.6	17	T3N0M0	3	37.7
18	T3N2M0	2	45.5	18	T3N0M0	3	44.0
19	T3N0M0	4	5.2	19	T3N1M0	1	53.1
20	T3N2M1	3	−8.2	20	T4N0M0	3	40.3
21	T4N1M0	4	−15.7				
22	T3N0M0	2	48.6				
23	T3N0M0	1	68.4				
24	T3N2M0	2	45.6				
25	T3N2M0	2	46.7				
26	T3N1M0	4	−7.1				

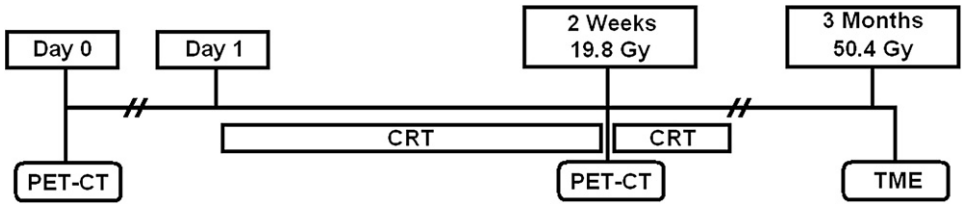

Fig. 1. Study scheme for the assessment of early metabolic response during pre-operative treatment with chemoradiotherapy (CRT). All included patients underwent fluorodeoxyglucose (FDG) positron emission tomography (PET) computed tomography (CT) imaging at two time points: prior to the start of treatment and after two weeks of treatment.

Additionally, all PET data were normalized for the blood glucose level measured shortly before FDG administration (15).

PET analysis

For each PET scan, the tumor was automatically delineated using SUV thresholding with the threshold (percentage of SUV_{max} within the tumor) depending on the tumor-to-background signal ratio with the gluteus muscle selected as relevant background (16, 17). Dedicated software (TrueD VC60, Siemens Medical, Erlangen, Germany) was used to calculate the maximum FDG uptake (SUV_{max}) within the tumor. Subsequently, a response index, indicating the percentage reduction relative to the pre-treatment measured value, was calculated.

Pathological tumor response

For each tumor, the pathological treatment response was evaluated by determination of the tumor regression grade (TRG) as proposed by Mandard (18). All tumors were retrospectively classified by an experienced pathologist (R.R.), who was blinded for the PET data, as follows: TRG1, complete tumor response; TRG2, residual cancer cells scattered through fibrosis; TRG3, an increased number of residual cancer cells, with predominant fibrosis; TRG4, residual cancer outgrowing fibrosis; TRG5, no regressive changes within the tumor. Based on the TRGs, the patients were grouped into pathological responders (TRG1, 2) and nonresponders (TRG 3–5).

Response prediction and validation

For 30 of the included patients, the metabolic and pathological treatment responses were correlated using ROC curve analysis. From the ROC curve, a cutoff value for the percent reduction of SUV_{max} within the tumor after 2 weeks of chemoradiotherapy (CRT) treatment was selected to differentiate pathological responders from non-responders. When selecting this cutoff value, a high specificity was preferred over a high sensitivity to avoid pathological nonresponders from being false positively predicted as pathological responders, resulting in possible undertreatment of pathological nonresponding patients. Next, the applicability of the selected cutoff value was validated for new patients (n = 21), imaged and treated under identical conditions as the patients on which the predictive model was based.

Statistical Analysis

Statistical analyses were performed using SPSS (version 15.0; SPSS Inc., Chicago, IL).

Comparisons of related measurements were performed using a Wilcoxon signed-rank test and ROC analysis was performed to evaluate the optimal cutoff value of SUV_{max} reduction to differentiate pathological responders from nonresponders.

RESULTS

Peritumoral inflammatory responses

From the first patient group (n = 30), 4 patients presented with a peritumoral inflammatory response, visually observed from the PET scan performed at the end of the second week of treatment. Also for the second patient group (n = 21), used for validation of the predictive model, 1 patient presented with a peritumoral inflammatory response. Because inflammatory cells are known to avidly consume glucose, all patients with a peritumoral inflammatory response were excluded from further analysis to prevent an underestimation of the metabolic treatment response of the tumor. When delineating the tumor using automatic SUV thresholding, an increase of the PET-positive tissue volume was found after 2 weeks of CRT treatment for the previously mentioned patients (Fig. 2). The increase of the PET-positive tissue volume is a clear indication of a peritumoral inflammatory response, since an increase of the volume of the malignancy is not to be expected during preoperative CRT treatment. Also, for these patients, a more diffuse FDG uptake was observed after 2 weeks of treatment with a decreased tumor-to-background signal ratio resulting in a less clear PET-based distinction between malignant and nonmalignant tissue (Fig. 2). All visually observed peritumoral inflammatory responses after 2 weeks of treatment were confirmed after pathological examination of the resected specimen.

Response prediction

For the first patient group, an average reduction of SUV_{max} within the tumor of 33.6 ± 25.8% ($p < 0.001$) was observed after 2 weeks of CRT (Fig. 3, Table 1). The SUV_{max} reduction within the tumor was correlated with the pathological response by ROC curve analysis, resulting in an area under the curve of 0.98 (Table 2). From the resulting ROC curve, a cutoff value of 48% SUV_{max} reduction was selected to differentiate pathological responders from nonresponders, resulting in a specificity of 100% to prevent pathological nonresponders from being false positively predicted as pathological responder (Fig. 4). However, for this cutoff value, a sensitivity of 64% was found, with 4 pathological responding patients to be false negatively predicted as pathological nonresponding (Fig. 4).

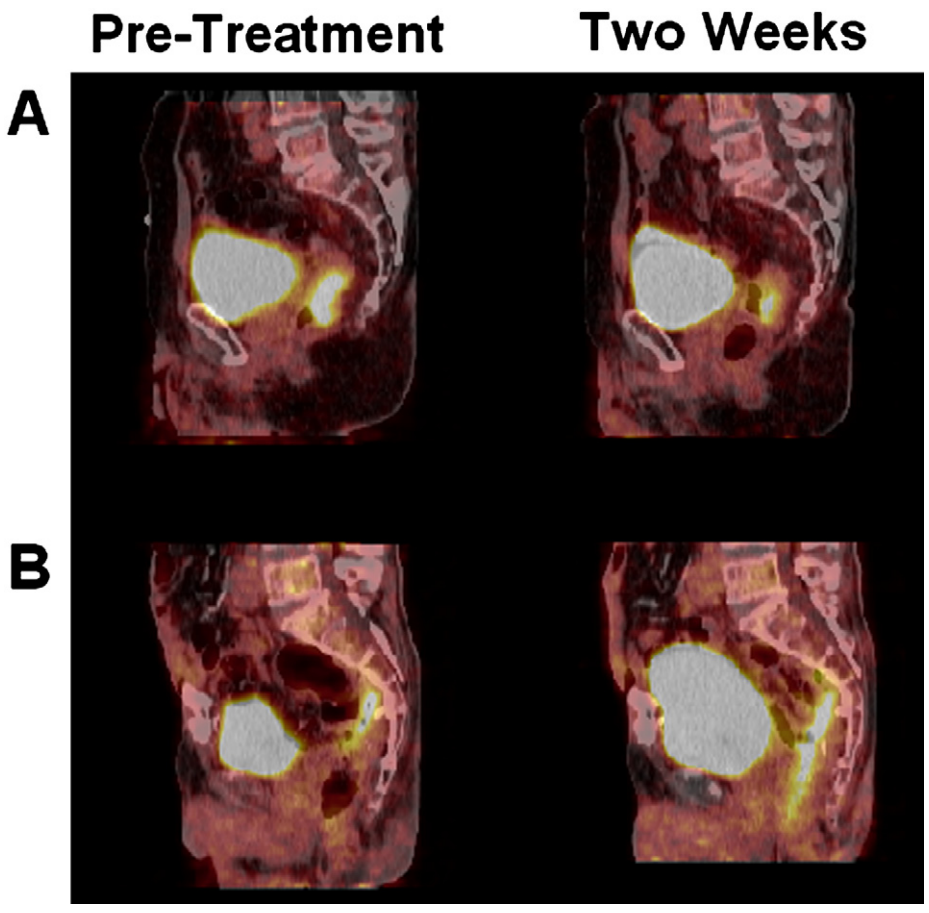

Fig. 2. Fluorodeoxyglucose (FDG) positron emission tomography (PET) computed tomography (CT) images at both PET-CT imaging time points for respectively a representative patient (A) and a patient presenting with a pathological reported peritumoral inflammatory response (B).

Validation

Also for the second patient group, a significant reduction of SUV_{max} within the tumor (32.3 ± 27.0%, $p = 0.001$) was found after 2 weeks of CRT (Fig. 3, Table 1). When applying the ROC curve based cutoff value of 48% to differentiate pathological responders from nonresponders, a specificity and sensitivity of, respectively, 93% and 83% was found, with only one of the pathological nonresponding patients (TRG3) being predicted false positively as pathological responding, whereas one pathological responder (TRG1) was predicted false negatively as being a pathological nonresponder (Fig. 4).

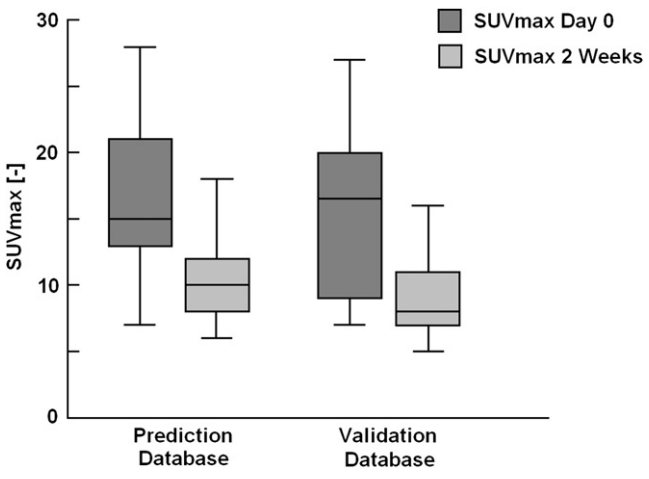

Fig. 3. Boxplots of maximum standardized uptake value (SUV_{max}) within the tumor at both positron emission tomography (PET) computed tomography (CT) time points for both patient groups, with the dark and light gray boxes presenting, respectively, the pretreatment SUV_{max} within the tumor and the SUV_{max} after 2 weeks of chemoradiotherapy.

DISCUSSION

Response predictive models based on changes of the metabolic activity of the tumor, assessed with repeated FDG-PET-CT imaging, were presented to result in accurate predictions of the pathological treatment response (1–14). However, proper validation of published PET-based response predictive models has not yet been performed. This is the first study performing a validation of a PET-based response prediction model using a SUV cutoff value to differentiate pathological responders from nonresponders. Validation of such response predictive models is required to ensure whether the presented model is applicable on patients who are not included in the patient group on which the model is based. When using a PET-based response prediction model for the differentiation of pathological responders

Table 2. Overview of average metabolic response (RI SUV_{max}) as assessed with fluorodeoxyglucose (FDG) positron emission tomography (PET) imaging, relative to the tumor regression grade (TRG)

	RI SUV_{max}
TRG 1	59.4 ± 9.4%; range, 45.3−70.4%
TRG 2	53.2 ± 10.5%; range, 38.9−69.4%
TRG 3	26.7 ± 22.9%; range, −11.8−54.4%
TRG 4	13.0 ± 20.4%; range, −19.9−45.1%
TRG 1–2	56.1 ± 10.2%; range, 38.9−70.4%
TRG 3–5	20.5 ± 22.5%; range, −19.9−54.4%

and nonresponders, the cutoff value (percent reduction of the FDG uptake within the tumor) used to differentiate responders from nonresponders should be chosen in such a way that as less nonresponding patients as possible are predicted false positively as pathological responding (12). This, to avoid undertreatment of false positively predicted pathological nonresponders when performing modifications of the treatment protocol based on the predicted treatment response. The selected ROC curve based cutoff value of 48% SUV_{max} reduction at the end of the second week of preoperative CRT (sensitivity 64%, specificity 100%) was applied on a second patient group, resulting in a sensitivity and specificity of respectively 83% and 93%, with one pathological nonresponder being predicted false positively as pathological responding. From these results, it was concluded that a PET-based predictive model using a cutoff value (percent reduction of SUV_{max} within the tumor) can be used to accurately predict the pathological treatment response for patients not included in the patient group on which the predictive model is based.

For this study, we defined patients with a TRG of 1 or 2 according to the Mandard criteria as being pathological responders and patients with a TRG 3–5 as pathological nonresponders. Earlier published literature proved patients with TRG1–2 to have a better prognosis compared to patients with TRG3–5 (19, 20). Patients presenting with a TRG1 or 2 were proven to have less chance on local failure, whereas they have an improved chance on metastasis- and disease-free survival as well as overall survival (20). Also, an extended time interval between preoperative CRT treatment and surgery has been presented to result in more pronounced tumor regression and downstaging, whereas a shorter time interval may interrupt ongoing of tumor necrosis (21–23). We believe that a PET-based response predictive model as presented in this manuscript could in the near future be helpful to identify those TRG1–2 patients to improve the tumor response by including these patients in a boost trial and/or apply an extended time interval between RT and surgery.

For some of the patients included in this study, a peritumoral inflammatory response was visually observed from the PET images acquired after the second week of CRT. As inflammatory cells are known to avidly consume glucose (analogs), peritumoral inflammatory responses can lead to an underestimation of the metabolic response of the tumor, ultimately resulting in false-negative predictions of pathological responders (10, 12, 24). Patients presenting with a (visually observed) peritumoral inflammatory response should not be included in the patient group on which a PET-based response predictive model is based and such PET-based response predictive model should not be applied for patient with a peritumoral inflammatory response.

Importantly, when predicting the pathological treatment response based on sequential PET data, standardization of the used PET imaging protocol concerning the PET image reconstruction algorithm, injected FDG activities and uptake periods, SUV calculation method, blood glucose level measurements and correction of the PET data for the blood glucose level is required (11, 16, 25–28).

In conclusion, this is the first validation of a PET-based model for the prediction of the pathological treatment response. The presented results prove that an accurate prediction of the pathological treatment response based on the reduction of SUV_{max} is possible already after 2 weeks of CRT treatment for patients treated and imaged identical to the patients on which the response predictive model is based.

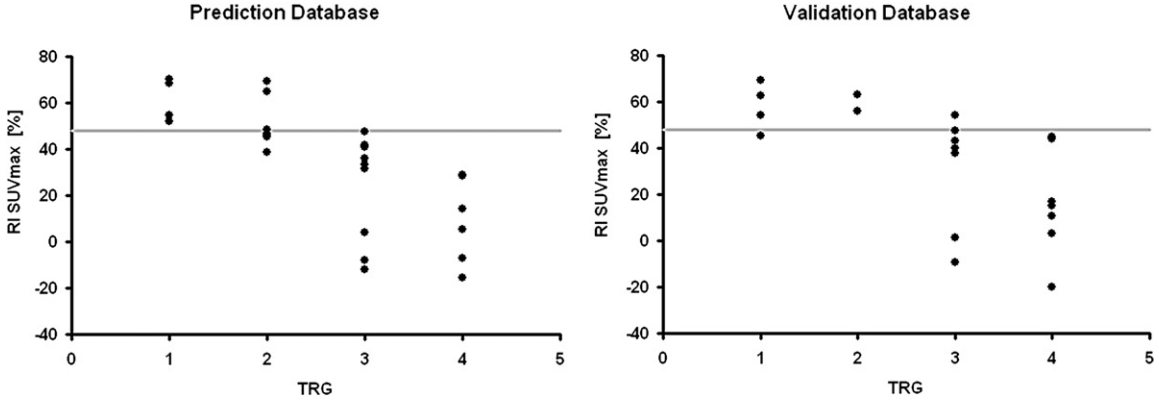

Fig. 4. Response indices (RI) of maximum standardized uptake value (SUV_{max}) after 2 weeks of preoperative chemoradiotherapy relative to the tumor regression grade (TRG) for both the prediction (left) and validation (right) database. The gray horizontal line indicates the receiver operating characteristic curve based cutoff value of 48% SUV_{max} reduction for the differentiation of pathological responders from nonresponders.

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